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INVITED EDITORIAL

Male androgen deficiency: a multisystem syndrome

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Androgens have important effects on multiple organ systems, which play critical roles in the regulation of a myriad of male sexual, somatic, and behavioral functions critical to lifelong health. Androgen deficiency is a multisystem syndrome, presenting with typical clinical features in association with a confirmed low serum testosterone level. The clinical presentation of androgen deficiency is modified by age and other patient-specific characteristics such as comorbidities, genetic, environmental, and sociocultural factors.

This special supplement of the *Asian Journal of Andrology* is intended to reflect the complexity of male androgen deficiency disorders. It provides a critical update on many recent advances in clinical and experimental aspects of male androgen deficiency, particularly those organ systems not traditionally or directly associated sexual or reproductive functions that contribute to the highly topical area of male health over the life course. While this issue highlights progress in male health, many important current knowledge gaps and areas of controversies are also emphasized.

In the first article of this issue, Nieschlag and Nieschlag[1] set the scene by painting a vivid historical panorama of androgen deficiency, highlighting the fact that male androgen deficiency has fascinated mankind since antiquity. While demonstrating the marked progress that has been made in this area in recent decades, they also provide a salient reminder of the lessons to be learnt from history, so as not to repeat mistakes from the past. The second article by Rana *et al.*,[2] fast-forwards to cutting-edge molecular biology, elucidating how genetically modified animal models underpin our mechanistic understanding of androgen action at the molecular level. Moving from mice to men, Vesper *et al.*,[3] focus on the very important topic of biochemical diagnosis of androgen deficiency. They discuss key issues in sex steroid assay technology and the recent efforts by the Center of Disease Control and Prevention, USA to improve and standardize the biochemical diagnosis of androgen deficiency. Høst *et al.*,[4] contribute a comprehensive update on Klinefelter's syndrome, the paradigmatic and commonest cause of pathological hypogonadism. They highlight the cardiometabolic and cognitive morbidity associated with this syndrome, and discuss recent progress in the management of fertility. Huhtaniemi[5] provides a lucid review of the challenges in the diagnosis and management of androgen deficiency in ageing men, which covers all the current controversies in an up-to-date, balanced fashion.

In the subsequent articles of this issue, androgen actions on nonsexual/reproductive organ systems are developed in more detail, with focus on musculoskeletal and cardiometabolic health as well as on sleep disorders.

One of the most important challenges facing the ageing population worldwide is age-related frailty with loss of functional independence. O'Connell and Wu[6] elegantly describe current concepts and definitions in age-related muscle loss (sarcopenia) and frailty, and discuss the mechanistic and potential therapeutic roles of androgens in this context. Twenty-five percent of men sustain a minimal trauma fracture in their lifetime, and hypogonadism is a common cause of osteoporosis. Laurent *et al.*,[7] review the roles of sex steroid in bone health, highlighting how cell-specific actions of individual sex steroids not only in different bone compartments, but also in other tissues such as the central nervous system shape our understanding of musculoskeletal health in a sex-dimorphic context. Androgens have important roles in cardiometabolic health. Ng Tang Fui *et al.*,[8] review the complex bidirectional relationship between obesity and low testosterone. They highlight recent insights that obesity-associated hypogonadism may be a functional state potentially reversible with weight loss, and discuss specific issues with testosterone therapy in obese men. Allan[9] thoughtfully scrutinizes the evidence for, and against, a causal role of low sex steroids in mediating insulin resistance and diabetes. She concludes that body composition, especially visceral fat is a critical determinant in the bidirectional relationship between androgens and glucose metabolism.

Safety concerns regarding the long-term risks of testosterone therapy on cardiovascular and prostate disease remain uncertain and controversial. This is due to the current lack of adequately designed and powered clinical trials to assess the effects of testosterone therapy on cardiovascular events or prostate cancer. Yeap[10] comprehensively and critically dissects the available evidence base on the relationship of sex steroids with cardiovascular disease. He also reviews the data suggesting both beneficial as well as harmful effects of testosterone treatment on cardiovascular health, calling for further research in this area. Cooper and Page[11] similarly highlight the need for long-term intervention trials to clarify effects of androgens on prostate health. They beautifully tie together epidemiological, mechanistic, and short-term interventional studies to suggest that there is little evidence causally linking testosterone

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treatment achieving physiological testosterone levels to prostate cancer, stressing however that because of the absence of definitive data, current guidelines are appropriately conservative.

Given these diverse actions of androgens in many organ systems, some of which beneficial, some potentially harmful, targeting androgen actions to certain tissues such as muscle while avoiding activity in others, for example prostate is intuitively attractive. This has spawned the development of selective androgen receptor modulators (SARMs), the focus of the penultimate article in this special edition. Coss *et al.*,[12] provide a state-of-the art update of this rapidly evolving field, covering all aspects from pharmacodynamics and pharmacokinetics to the outcomes of early, phase 2 randomized controlled clinical trials. They conclude that ongoing phase 3 clinical trials should clarify whether SARMs have potential in the treatment of specific muscle wasting disorders such as that associated with cancer cachexia. However, they caution that several regulatory obstacles need to be overcome before their broader utility in male ageing can be explored.

While circulating testosterone displays circadian rhythmicity, relatively little is known about androgens and the regulation of sleep. Wittert[13] boldly steps into this new frontier succinctly summarizing the relationships of testosterone with sleep duration, quality, and architecture. He covers recent advances in normal physiology as well as in disordered sleep induced experimentally, in shift work, and obstructive sleep apnea.

It should be clear to the reader that, while androgen deficiency in men has become an important clinical topic and a vibrant field of research, many exciting opportunities remain for further research and therapeutic development towards improving men's health and quality of life. Male androgen deficiency is a global health issue with huge market potential and of particular importance in Asia, given the ageing population and the rapidly increasing number of obese men. It is our hope that this special edition will inspire not only budding and veteran andrologists, but also clinician-researchers from other fields to engage with this buoyant area of medical research, and that we can anticipate new scientific collaborations between academic andrology centers in the Asia-Pacific region, Australia, and elsewhere.

REFERENCES

1 Nieschlag E, Nieschlag S. Testosterone deficiency: a historical perspective. Asian J Androl 2014; 16: 161–8.
2 Rana K, Davey RA, Zajac JD. Human androgen deficiency: insights gained from androgen receptor knockout mouse models. Asian J Androl 2014; 16: 169–77.
3 Vesper HW, Botelho JC, Wang Y. Challenges and improvements in testosterone and estradiol testing. Asian J Androl 2014; 16: 178–84.
4 Høst C, Skakkebæk A, Groth KA, Bojesen A. The role of hypogonadism in Klinefelter syndrome. Asian J Androl 2014; 16: 185–91.
5 Huhtaniemi I. Late-onset hypogonadism;current concepts and controversies of pathogenesis, diagnosis and treatment. Asian J Androl 2014; 16: 192–202.
6 O'Connell MD, Wu FC. Androgen effects on skeletal muscle: implications for the development and management of frailty. Asian J Androl 2014; 16: 203–12.
7 Laurent M, Antonio L, Sinnesael M, Dubois V, Gielen E, et al. Androgens and oestrogens in skeletal sexual dimorphism. Asian J Androl 2014; 16: 213–22.
8 Ng Tang Fui M, Dupuis P, Grossmann M. Lowered Testosterone in Male Obesity: Mechanisms, Morbidity and Management. Asian J Androl 2014; 16: 223–31.
9 Allan CA. Sex steroids and glucose metabolism. Asian J Androl 2014; 16: 232–8.
10 Yeap BB. Sex steroids and cardiovascular disease. Asian J Androl 2014; 16: 239–47.
11 Cooper LA, Page ST. Androgens and prostate disease. Asian J Androl 2014; 16: 248–55.
12 Coss CC, Jones A, Hancock ML, Steiner MS, Dalton JT. Selective Androgen Receptor Modulators for the Treatment of Late Onset Male Hypogonadism. Asian J Androl 2014; 16: 256–61.
13 Wittert G. The relationship between sleep disorders and testosterone in men. Asian J Androl 2014; 16: 262–5.

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